PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 16 SEPTEMBER 2005
see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/001099	23.03.2004	26.03.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/505, C07D405/06, C07D309/10, C07D309/30

Applicant
AVECIA PHARMACEUTICALS LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/001099

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/001099

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,4
	No:	Claims	3,5
Inventive step (IS)	Yes:	Claims	1,2,4
	No:	Claims	3,5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV.

The separate inventions/groups of inventions are:

A) Claims 1,4,5

Present compounds of formula 5 and processes for their synthesis comprising the step of coupling present compounds of formula 3 and 4.

B) Claim 2

Process for the synthesis of present compounds of formula 2 from present compounds of formula 1.

C) Claim 3

Process for the synthesis of present compounds of formula 3 from present compounds of formula 2.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present subject matter is directed towards the synthesis of present pyrano derivatives of formula 2 and 3, and to the synthesis of present lactone derivatives of formula 5 as intermediates for the synthesis of Rosuvastatin. For the purposes of unity of invention, Rule, 13.1 PCT stipulates that an international application must relate to one invention only or to a group of inventions so linked as to form a single general (inventive) concept. After non-exhaustive, preliminary documentary search it appears that compounds 2, 3 and 5 are know in the art (cf. Tetrahedron, vol. 46, 1990, 6731-6740; US2003/232989). In view of the said prior art, the problem underlying the present application may have been the provision of further process for the synthesis of Rosuvastatin. Compared with the prior art, divergent solutions to this problem could be defined as subject-matter of the claims of the present application, based on the reaction pathways chosen and reactants used. This could for example mean that the following different approaches would have been considered by the skilled person: 1) process for the provision of present intermediates of formula 2; 2) process for the provision of present intermediates of formula 3 using 2 as starting material; 3) process for the provision of present intermediates of formula 5 using 3 as starting

material. The only common feature between these three processes is present compound of formula 3. This cannot however be considered as being a special technical features within the meaning of Rule 13.1 PCT, since, being known from Tetrahedron, vol. 46, 1990, 6731-6740, it makes no contribution to the art. For the same reason, compound 2 cannot be considered a special technical feature - within the meaning of Rule 13.1 PCT - linking the above mentioned approaches 1 and 2. Consequently there is lack of unity within the meaning of rule 13 PCT and the different inventions, not belonging to a common inventive concept, have to be formulated as different subjects pursuant to Article 17(3) (a) PCT.

Re Item V.

Reference is made to the following documents:

D1: US 2003/232989 A1 (ANTONS STEFAN ET AL) 18 December 2003 (2003-12-18)

D2: WO 01/85702 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; HILL, STEVEN, JAMES; LENZ, EVA) 15 November 2001 (2001-11-15)

D3: BARTH M ET AL: "TOWARDS A NEW TYPE OF HMG-COA REDUCTASE INHIBITOR" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 46, no. 19, 1990, pages 6731-6740, XP000942264 ISSN: 0040-4020

D4: DURAND-REVILLE, THOMAS ET AL: "Highly Selective Entry to the Azadirachtin Skeleton via a Claisen Rearrangement/Radical Cyclization Sequence" ORGANIC LETTERS , 4(22), 3847-3850 CODEN: ORLEF7; ISSN: 1523-7060, 2002, XP002343425

D5: YANG, YUH LIN ET AL: "Mevinic acids and analogs: preparation of a key chiral intermediate" TETRAHEDRON LETTERS , 23(42), 4305-8 CODEN: TELEAY; ISSN: 0040-4039, 1982, XP002343426

D6: ROSEN T ET AL: "SYNTHETIC AND BIOLOGICAL STUDIES OF COMPACTIN AND RELATED COMPOUNDSSYNTHESIS OF THE LACTONE MOIETY OF COMPACTIN" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 49, 19 October 1994 (1994-10-19), pages 3994-4003, XP000996454 ISSN: 0022-3263

D7: BECK G ET AL: "Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 1. Lactones of Pyridine- and Pyrimidine-Substituted 3,5-Dihydroxy-6-heptenoic (-heptanoic) Acids" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 33, no. 1, 1990, pages 52-60, XP002324910 ISSN: 0022-2623

D8: US-A-4 677 211 (JEWELL, JR. ET AL) 30 June 1987 (1987-06-30)

D9: US-A-4 625 039 (JEWELL, JR. ET AL) 25 November 1986 (1986-11-25)

D10: US-A-4 474 971 (WAREING ET AL) 2 October 1984 (1984-10-02)

GROUP A

NOVELTY (Article 33(2) PCT)

D1 discloses documents (cf claim 3) which are encompassed by present claim 5. Said claim is therefore not novel over D1.

Present claim 1 and 4 differ from D1 on account of the use of compounds of formula 3 and 4 as starting material for the synthesis of present compound of formula 5.

The present subject matter differs from D2 on account of the use of present lactone of formula 3 as starting material for the synthesis of present compound 5.

Documents D3-D10 are not directed towards the synthesis of present compounds of formula 5.

INVENTIVE STEP (Article 33(3) PCT)

The present subject matter is directed towards the synthesis of Rosuvastatin.

D1 is considered to be the closest prior art and discloses the synthesis of several aromatic aldehydes, Rosuvastatin and present compound of formula 5 among the others.

The present subject matter differs from D1 on account of the synthetic step where present compounds 4 and 3 are coupled to give present compound 5.

The problem to be soled by the present subject matter vis-à-vis D1 is considered to be the provision of a novel process for the synthesis of 5.

The problem has been solved by reacting the phosphonate or phosphonium derivative of the pyrimidine compound of formula 4 with the aldehyde derivative of the lactone of formula 3. In the process according to D1, an aldehyde derivative of, *inter alia*, a pyrimidine compound is reacted with an open chain phosphonate or phosphonium derivative. Present compound of formula 5 is then obtained by cyclisation of the side chain of the pyrimidine derivative obtained (cf D1, page 4, paragraphs 23-33).
Phosphonate derivatives according to present formula 4 are used in D2 (cf page 4, scheme 1). However, said derivative are reacted with the "open form" (cf scheme 1, compound IIE) of present lactone of formula 3. Although various protected forms of said "open form" are reported in D2 (e.g. scheme 1, compound IIE; scheme 2 compound E), there is no suggestion in D1 that the present lactone of formula 3 could be an alternative to the reactants (eg IIE or E) used in D1. Thus, it appears that the skilled person would have not found in the combined teaching of D1 and D2 any motivation to consider the coupling of present compounds 4 and 5 as a solution for the given problem. Accordingly, an inventive step can be acknowledged to present claims 1 and 4.

On the other hand, an inventive step cannot be acknowledged for present compounds of formula 5, since their use as intermediates in the synthesis of e.g. Rosuvastatin is known in the art (eg D1).

GROUP B

NOVELTY (Article 33(2) PCT)

D1-D2 do not discloses present compounds of formula 2.

The present subject matter differs from D3-D10 on account of the use of present compounds of formula 1 as the starting material for the synthesis of present compounds of formula 2.

INVENTIVE STEP (Article 33(3) PCT)

The subject matter of claim 2 is directed towards the synthesis of present compounds of formula 2 using compounds 1 as starting material.

D6 is considered to be the closest prior art and discloses the synthesis of lactone derivatives falling within the definition of present compounds of formula 2 using Tri-O-acetyl-glucal as the starting material.

The subject matter of present claim 2 differs from D6 on account of the use of present compound of formula 1 as starting material.

None of the quoted prior art documents disclose or even suggests that the present alcohol 2 could be obtained from the hydrolysis of the corresponding haloderivative 1. On the contrary, D5 and D6 disclose the "reversed" reaction, i.e. the provision of present compounds of formula 1 using alcohol 2 as the starting material.

Thus, it appears that the skilled person, facing with the problem of providing an alternative route to derivative 2, would have not considered the haloderivative 1 as a suitable starting material. Accordingly, an inventive step can be acknowledged for present claim 2.

GROUP C

Each of the documents D3-D10 discloses the synthesis of present compounds of formula 3 *via* the oxidation of the alcohol derivative of formula 2. Accordingly, present claim 3 does not fulfil the requirements of Articles 33(2) and 33(3) PCT.